II. Amendments to the Specification:

The amendments to the specification do not introduce new matter. The amendment suggested by the Examiner involving "PCT/US97/____" at page 50 in the original sequence listing was addressed in the Preliminary Amendment dated February 18, 1998.

III. Rejections Under 35 U.S.C. §112, Second Paragraph:

In item 9 of the Office Action, the Examiner rejected claims 2, 13, 14, 17, 18, 21 and 22 under 35 U.S.C §112, second paragraph and alleged that these claims were indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the subject matter Applicants regard as the invention.

Applicants amendments to the claims hereinabove clarify the subject matter of the invention and render this rejection moot.

IV. Rejections Under 35 U.S.C. §112, First Paragraph:

In item 10 of the Office Action, the Examiner rejected claims 13, 14, 17, 18, 21 and 22 because the specification allegedly fails to provide an enabling disclosure because the specification does not provide evidence that the claimed biological materials are known and readily available or reproducible or deposited is incomplete.

In response, Applicants maintain that the hybridomas designated HB10036 and HB 10460 have been deposited pursuant to the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purposes of Patent Procedure with the Patent Culture Depository of the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia, 20110–2209 USA.

Applicants maintain that during the pendency of the subject application, access to the ATCC Deposit will be afforded to one determined by the Commissioner to be entitled thereto under 35 USC §1114 and §122, and all restrictions on availability to the public of the materials

deposited under ATCC No. HB10036 and HB 10460 will be irrevocably removed upon the issuance of a patent from the subject application.

Furthermore, the above deposit will be maintained by the ATCC for a period of 30 years from the date of deposit or at least five years after the last request for a sample of the deposited material, whichever is longer. Where the ATCC cannot furnish samples of the above deposit for any reason, Applicants shall make a replacement deposit, of the material which was originally deposited, within three months of receiving the notification that the ATCC cannot furnish samples. All restriction on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent from the subject application.

In item 11 of the Office Action, the Examiner rejected claims 21 and 22 because the specification allegedly failed to provide an enabling disclosure.

Applicants respectfully traverse this rejection and point out that the amendments to the claims render this rejection moot.

V. Rejections Under 35 U.S.C. §102(b):

In item 13 of the Office Action, the Examiner rejected claim 1, 2, 5 and 7–10, under 35 U.S.C. §102(b), alleging that these claims were anticipated by Morgan et al. (WO 94/29351). As illustrated below, Applicants respectfully traverse this rejection because Morgan et al. do not teach or suggest methods for inhibiting immunoglobulin–induced toxicity by using antibodies having modifications in multiple toxicity associated domains.

A. The Claimed Invention

The claimed invention is directed to methods for inhibiting immunoglobulin–induced toxicity resulting from immunoglobulin immunotherapy in a subject. In this context Applicants disclose the use of antibodies having alterations in multiple toxicity associated domains so that the antibodies are no longer able to (1) mediate the antibody dependent cellular cytotoxicity

response or (2) activate complement. Moreover, Applicants establish that antibodies having alterations in multiple toxicity associated domains have a reduced toxicity *in vivo*.

At page 10, lines 8–15, Applicants discuss the definition of "multiple toxicity associated domains" where they teach:

> [A]s used herein the terms "multiple toxicity associated domains" means more than one discrete toxicity associated domain. As there appear to be at least two toxicity associated domains in the immunoglobulin molecule, one roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331, an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues in both of these domains. This definition excludes structural alterations targeting a single toxicity associated domain.

By utilizing antibodies which have alterations both in a toxicity associated domain in the C-terminal region of the CH2 domain (roughly localized to amino acids 310-331) as well as alterations in a toxicity associated domain in the N-terminal region of the CH2 domain (roughly localized to amino acids 231-238), Applicants provide a means of significantly inhibiting immunoglobulin–induced toxicity.

B. Morgan et al. (WO 94/29351)

Morgan et al. disclose methods which utilize antibodies where amino acid residues in the N-terminal domain of the CH2 region are altered so that the ability of the antibody to fix complement and bind FcR is altered as compared to unaltered antibody (see e.g. page 5, lines 11-16). In delineating this portion within the N-terminal domain of the CH2 region that is altered in their methods, Morgan et al., teach at page 4, lines 4-7:

> [W]e have found that the amino acid residues necessary for C1q and FcR binding of human IgG1 are located in the N-terminal region of the CH2 domain, residues 231 to 238, using a matched set of engineered antibodies based on the anti-HLA DR antibody L243.

Morgan et al. do not teach or suggest the use of antibodies having alterations in multiple toxicity associated domains.

C. The Claimed Invention Cannot be Anticipated by Morgan et al. (WO 94/29351)

As illustrated above, Morgan et al. teach methods utilizing antibodies having alterations in a single toxicity associated domain and fail to teach or suggest antibodies having alterations in multiple toxicity associated domains. In addition, while Morgan et al. utilize antibodies having mutations in the C–terminal domain of CH2 in assays which evaluate the antibodies of their invention (see e.g. Figure 16), they teach that it is the alterations in the N–terminal region of CH2 that reduce toxicity. In particular, Morgan et al. direct the skilled artisan to target residues in amino acid positions 231 to 238 because of their fundamental role in complement activation (see e.g. Page 4, lines 4-7). Moreover, Morgan et al. specifically question the biological significance of other amino acid residues with the CH2 region, noting that residues 318, 320 and 322 in the C-terminal domain, while possibly being involved in the complement cascade, are not sufficient for complement activation (see e.g. page 4, line 5).

In addition to failing to teach or suggest antibodies having alterations in multiple toxicity domains, Morgan et al. cannot anticipate Applicants' methods for inhibiting immunoglobulin–induced toxicity because this reference provides no data on immunoglobulin–induced toxicity resulting from immunoglobulin immunotherapy. In particular, while Morgan et al. disclose experiments showing how alterations in the N–terminal region of CH2 effect the ability of antibodies to fix complement or mediate antibody dependent cellular cytotoxicity *in vitro,* they provide no data on actually inhibiting immunoglobulin–induced toxicity. Moreover, Morgan et al. fail to provide any information on which of the multiple toxicity associated domains in CH2 control immunoglobulin–induced toxicity. For this reason, one skilled in the art cannot determine which alterations in CH2 are associated with a reduction in immunoglobulin induced toxicity. In contrast, Applicants' *in vivo* data clearly shows that alterations in multiple toxicity

associated domains in the constant region inhibit the immunoglobulin–induced toxicity that results from immunotherapy (see e.g. Example 3).

As Morgan et al. fail to either teach or suggest methods for inhibiting immunoglobulin–induced toxicity by using antibodies having modifications in multiple toxicity associated domains or provide any insight on which alterations in CH2, if any, are associated with a reduction in immunoglobulin–induced toxicity, this reference cannot anticipate the claimed invention.

VI. Rejections Under 35 U.S.C. §103(a):

In item 15 of the Office Action, the Examiner rejected claims 3, 4, 6 and 11–22 under 35 U.S.C. §103(a), alleging that these claims were unpatentable over Morgan et al. (WO 94/29351) as applied to claim 1 or 2, and in view of Yelton et al. (U.S. Patent No. 5,792,456) or Muroi et al. (Blood 79: 713–719, 1992) and Gilles et al. (Human Antibodies and Hybridomas 1: 47–54, 1990).

As illustrated above, Morgan et al. do not teach or suggest methods for inhibiting immunoglobulin–induced toxicity by using antibodies having modifications in multiple toxicity associated domains. The deficiencies in Morgan et al. are not remedied by the teachings of Gilles et al., Yelton et al. or Muroi et al.

While Gilles et al. provides a method for mutating the constant region of a human gamma chain and note that these mutants exhibit little ADCC or CDC activity, a combination of this reference with Morgan et al. does not teach that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin–induced toxicity. Moreover, because the biological significance of the amino acid residues in the C-terminal domain is disparaged in Morgan et al., one skilled in the art would be disinclined to combine these references in the manner suggested by the Examiner. In addition, even if one was to try to combine such disparate references, the resulting combination would not generate the claimed invention. Therefore, the claimed invention cannot be obvious in light of these references. For this reason, Applicants respectfully request the withdrawal of this rejection.

While Yelton et al. provides teachings about mutant BR96 as a composition of matter and its use in some contexts, this reference does not disclose Applicants' claimed methods for inhibiting immunoglobulin–induced toxicity. In particular, while the Yelton et al. note that functional equivalents of mutant BR96 antibody which do not include the Fc region do not exhibit ADCC or CDC properties, a combination of this reference with Morgan et al. does not teach that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin–induced toxicity. Moreover, because the biological significance of the amino acid residues in the C-terminal domain is disparaged in Morgan et al., one skilled in the art would be disinclined to combine these references in the manner suggested by the Examiner. In particular, even if one was to try to combine such disparate references, the resulting combination would not generate the claimed invention. Therefore, the claimed invention cannot be obvious in light of these references. For this reason, Applicants respectfully request the withdrawal of this rejection.

Muroi et al. simply disclose antibodies that recognize and bind to Le^x. This reference does not overcome the deficiencies in the other references cited by the Examiner and a combination of these references does not teach or suggest that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin–induced toxicity. For this reason, Applicants respectfully request the withdrawal of this rejection

In item 16 of the Office Action, the Examiner rejected claims 28–31 under 35 U.S.C. §103(a), alleging that these claims were unpatentable over Morgan et al. (WO 94/29351) in view of Yelton et al. (U.S. Patent No. 5,792,456).

Applicants respectfully traverse this rejection and point out that Morgan et al. do not teach or suggest methods for inhibiting immunoglobulin–induced toxicity by using antibodies having modifications in multiple toxicity associated domains. As illustrated above, this deficiency in Morgan et al. is not remedied by the teachings of Yelton et al. For this reason, Applicants respectfully request the withdrawal of this rejection

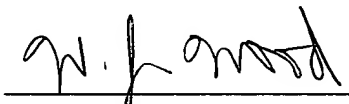
VII. Conclusion:

In light of the forgoing remarks, Applicants assert the pending claims are in condition for allowance. Notice of such allowance is solicited.

The Examiner is invited to telephone the undersigned attorney for clarification of any of the remarks above, or to otherwise further the prosecution of this case.

If any fee, other than the one-month extension of time fee of $110.00 is deemed necessary in connection with the filing of this Amendment, the Patent Office is authorized to charge the fee(s) to Deposit Account No. 13-2724.

Respectfully submitted,



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